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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/662,345	09/16/2003	Levon Arakelyan	Q71975	2068

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EXAMINER	
CLOW, LORI A	

ART UNIT	PAPER NUMBER
1631	

NOTIFICATION DATE	DELIVERY MODE
11/23/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/662,345	ARAKELYAN ET AL.	
	Examiner	Art Unit	
	LORI A. CLOW	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *10 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11 and 13-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/6.2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

In view of the After Final response filed 22 October 2009 and upon further consideration of the prior art and the instantly recited claims PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

Applicants' response, filed 22 October 2009, has been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application. The After Final claim amendments have been entered.

Claims 1-21 are currently pending. Claims 10 and 12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 20 April 2006.

Claims 1-9, 11, and 13-21 are examined herein.

Information Disclosure Statement

It is noted that in the Office Action of 2 August 2006 Reference 1 of the IDS submitted 6 January 2004 was not considered. However, upon further search, a date has been found for the reference and updated on the IDS and has been considered herein. Reference 22 has not been considered as no publication date can be found. Please find a copy of PTO form 1449, updated with publication date information, attached hereto.

Claim Objections

Claim 1 is objected to because of the following informalities: Claim 1, step d) recites, "one dose escalation steps". This is incorrect grammatically and should read "dose escalation step". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9, 11, 13, 14 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, step f) recites, "checking the drug for cumulative effects after administration and providing this information to the computer model". It is unclear as to how one would check the drug for cumulative effects. Perhaps Applicant intends the claim to read, "checking the patient for cumulative drug effects after administration". Clarification through clearer claim language is requested.

Claim 1, step j) recites, "performing at least one phase III clinical trial for step h) chosen clinical indication by step i) chosen regimens". It is unclear what is intended by this step. Is the phase III clinical trial performed such that the clinical indication from step h) is assessed by implementing the optimal regimen from step i)? Clarification through clearer claim language is requested.

Claim 1, step k) recites, "performing at least one phase IV clinical trial for post-marketing subpopulation analysis and long term product safety". It is unclear as to the relationship between step k) and the previous method steps. It appears as if claim language tying the steps together has been omitted. For instance, is step k) performed based upon the results of the previous method steps (i.e. the results from the Phase I, II, and III trial data)? Further, what is the outcome of performing step k)? Is it to determine rare side effects or unexpected drug interactions based on the previous phase I, II, and III results? Clarification through clearer claim language is requested.

Claim 20 recites, "administering at least a single dose of a drug to obtain data from performing". Further, it is unclear as to how "to obtain data from performing a phase IV clinical trial" in the context of the instant claim. Perhaps Applicant intends the claim to read, "to obtain data for performing a phase IV clinical trial". It is unclear as to what the drug is being administered to (e.g., an animal, a human). Clarification is requested.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9, 11, and 13-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over the CDER Handbook (from Department of Health and Human Services, FDA. http://Available at: http://www.fda.gov/cder/handbook/ The CDER Handbook. Revised March 16, 1998; IDS reference), in view of Berry (BioPharmaceutical Report (2001) Vol. 9, No. 2, Winter, pages 1-11; IDS Reference) and in further view of view of Holford et al. (Ann. Rev. Pharmacol. Toxicol. (2000) Vol. 40, pages 209-234) and Veyrat-Follet et al. (Clin. Phamacol. Ther. (2000) Vol. 68, pages 677-687; IDS Reference). This is a new grounds of rejection based upon further consideration of the instant claims.

The instant claims are drawn to a method of performing interactive clinical trials for testing a new drug for cancer studies comprising performing a pre-clinical phase to determine a computer model; obtaining data for the computer model; performing a phase I clinical trial in parallel with running computer simulations; adjusting the model based on the clinical trial and

increasing the dose; calculating dose escalation for maximum tolerated dose, minimum effective dose and recommended dose; performing multiple simulations using the computer model; determining an optimal regimen for a phase II trial; performing the phase II trial; performing a phase III trial and finally performing a phase IV trial.

In regard to claims 1, 13, 15-19 the CDER handbook is a handbook for new drug development guidelines as determined by the Food and Drug Administration of the United States (FDA). The handbook outlines the procedures for the new drug development process in which pre-clinical research is conducted which includes animal testing and the progression from the pre-clinical stage to Phase I, II, and III clinical studies and accelerated drug development (page 4 figure). In pre-clinical research studies, data from *in vitro* and *in vivo* laboratory animal studies is complied and new pre-clinical studies are designed to provide evidence of safety for administration to human subjects (page 5, paragraph 2 and 3). From the pre-clinical trial data, data are used to provide a decision such that it is safe to proceed with human clinical trials. In Phase I studies, the initial introduction of the new drug into humans is provided. In Phase I studies, drug metabolism, structure-activity relationships and the mechanism of action is determined (page 8, paragraph 2). In Phase II studies, clinical studies on drug effectiveness are conducted, as well as short-term side effect and risks (page 8, paragraph 4). In Phase III studies, data from Phase II studies is used further data regarding effectiveness is obtained (page 8, paragraph 5).

The CDER Handbook also outlines the determination of a stop-trial decision (page 17, paragraph 1) if the risk is determined too great (claims 3 and 9).

To further detail the nuances of clinical trial testing steps, Berry teaches that Phase I clinical trials involve dose escalation and the determination of a maximum tolerated dose (MTD) (page 3, column 2). Phase II trials involve optimal dose determination for determining the move to Phase III trials (page 4, column 1). Berry also teaches stopping trial if it is determined that the drug is not sufficiently effective to continue (page 4, column 1). Berry further teaches models for clinical trials in which algorithms may be adjusted in response to data during the trial and between trials (page 4, column 2) (claims 2, 6)

Neither the CDER Handbook nor Berry specifically teaches determining a computer model for clinical trial design. However, Holford et al. teach computer simulations for clinical trials for drug development purposes (abstract). Holford teaches that computer simulation is the process of building a mathematical model that mimics a real-world situation and then using the model to conduct experiments in order to describe, explain, investigate, and predict behavior of that situation (page 209, Introduction). Holden teaches the modeling based on dose concentration effect relationships in early drug development (page 210 and page 213). Holden further teaches that simulations can be used to define responses across trials (page 217) and in all phases of clinical trials from discovery to Phase IV (page 230) (claim 14, 20, 21).

To further illustrate the implementation of a clinical trial simulation, Veyrat-Follet et al. teach that clinical trial simulation is based on pharmacokinetic and pharmacodynamic models for the streamlining drug development (page 677, column 1). In regard to claims 4, 5, 7, 8, and 11, Veyrat-Follet et al. teach the determination of subpopulations based on clinical trial simulations in different clinical Phase II trials. A subpopulation of high AGG was further studied for alternative dosing regimens (page 678, column 1 and 2). Results from the clinical simulation

were then compared to actual clinical trial results to determine the dosing regimen for Phase III (page 678, column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have implemented the guidelines for clinical trials as outlined by the FDA in the CDER handbook which moves from pre-clinical trials to Phase IV for any given set of newly tested drugs with the further specifics of Phase II and III trial design as described and taught by Berry and include computer simulation for each step of the trial design as taught by Holford and by Veyrat-Follet for a streamline and efficient design. One would have been motivated to do so, as Berry teaches that a model algorithm that guides trial conduct makes dose decisions and recommendations to continue the trial or stop the trial or shift the focus of the trial to a confirmatory stage (page 4, column 2). As such one would have been motivated to include simulations along with real time trial data, working in parallel to assure a cost effective, streamline drug development process. Further, Holford states that computer simulation can maximize the amount of pertinent information gained in the clinical trial process and that simulation is applicable in many areas of the trial process (page 210). Further, Holford teaches that trial design is a dynamic plan and that as new information is gained, modifications are made (page 213) and that simulation and modeling are important for trials commencing in the preclinical stages and should be fully integrated in to all subsequent clinical phases (page 230).

No claims are allowed.

Conclusion

The outstanding rejections under 35 USC 101 over claims 15-21 are hereby withdrawn in view of the claim amendments reciting, "administering at least a single dose of a drug *in vitro* or *in vivo*". It is noted that the outstanding rejections under 35 USC 101 pertaining to claims 1-14 had previously been withdrawn in the Advisory Action of 10 September 2009.

The rejection raised in the Advisory Action of 10 September 2009 pertaining to 35 USC 112, 2nd is withdrawn in view of the claim amendments.

Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The Central Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lori A. Clow, Ph.D., whose telephone number is (571) 272-0715. The examiner can normally be reached on Monday-Friday from 10 am to 6:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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November 19, 2009
/Lori A. Clow, Ph.D./
Primary Patent Examiner
Art Unit 1631